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Abstract: Kazakhstan is highly endemic for echinococcosis. Both *Echinococcus granulosus* and *E. multilocularis* are distributed widely in the country. Official records of human cystic echinococcosis over the past 5-10 years suggest a stable incidence of approximately 800 – 1000 cases per year which is 5 cases per 100,000 per year. This followed a rapid increase in the incidence following the dissolution of the Soviet Union. Between 2007 and 2013, 5949 cases were reported in the national surveillance data. The prevalence in sheep, based on slaughter house studies suggests between 30 and 50% of sheep are infected with hydatid cysts whilst cattle have a prevalence of approximately 7%. Rural dogs have a high prevalence of infection of between 5 and 10% with shepherd dogs having prevalences of over 20%. G1 and G6/7 strains of *E. granulosus* have been isolated from dogs in Kazakhstan. Wolves are also infected with one prevalence estimate of approximately 20%. The incidence of human alveolar echinococcosis is less clear although estimates from Kazakhstani expatriates living in Germany and the hospital records of a single referral centre in Almaty suggest 34 or 130 cases per year (or an annual incidence of 0.20 or 0.76 cases per 100,000) respectively could be occurring in Kazakhstan. Studies suggest that in some rural dog populations the prevalence may be about 5%. The parasite is widely distributed in foxes and small mammals through much of Kazakhstan.

DOI: <https://doi.org/10.1017/S0022149X15000425>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-113287>

Journal Article

Accepted Version

Originally published at:

Abdybekova, A; Sultanov, A; Karatayev, B; Zhumabayeva, A; Shapiyeva, Z; Yeshmuratov, T; Toksanbayev, D; Shalkeev, R; Torgerson, Paul R (2015). Epidemiology of echinococcosis in Kazakhstan: an update. *Journal of Helminthology*, 89(6):647-650.

DOI: <https://doi.org/10.1017/S0022149X15000425>

Epidemiology of echinococcosis in Kazakhstan – an update

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Abstract

Kazakhstan is highly endemic for echinococcosis. Both *Echinococcus granulosus* and *E. multilocularis* are distributed widely in the country. Official records of human cystic echinococcosis over the past 5-10 years suggest a stable incidence of approximately 800 – 1000 cases per year which is 5 cases per 100,000 per year. This followed a rapid increase in the incidence following the dissolution of the Soviet Union. Between 2007 and 2013, 5949 cases were reported in the national surveillance data. The prevalence in sheep, based on slaughter house studies suggests between 30 and 50% of sheep are infected with hydatid cysts whilst cattle have a prevalence of approximately 7%. Rural dogs have a high prevalence of infection of between 5 and 10% with shepherd dogs having prevalences of over 20%. G1 and G6/7 strains of *E. granulosus* have been isolated from dogs in Kazakhstan. Wolves are also infected with one prevalence estimate of approximately 20%

The incidence of human alveolar echinococcosis is less clear although estimates from Kazakhstani expatriates living in Germany and the hospital records of a single referral centre in Almaty suggest 34 or 130 cases per year (or an annual incidence of 0.20 or 0.76 cases per 100,000) respectively could be occurring in Kazakhstan. Studies suggest that in some rural dog populations the prevalence may be about 5%. The parasite is widely distributed in foxes and small mammals through much of Kazakhstan.

Keywords

Echinococcus granulosus, *Echinococcus multilocularis*, alveolar echinococcosis, cystic echinococcosis, epidemiology

Introduction

Kazakhstan is a large landlocked country in the northern hemisphere of greater than 2.4 million square kilometres. Favorable natural and climatic conditions of Kazakhstan and large areas of pastures at 180 million hectares has resulted in animal husbandry as a traditional occupation of the indigenous population. Presently there are approximately 6.5 million cattle, 17.5 million sheep, 2 million horses and 172,000 camels. This large animal population potentially favours the transmission of *Echinococcus granulosus* and infection is now widespread in the animal population (Shaikenov *et al.*, 2003; Torgerson *et al.*, 2003).

At the end of last decade of the 20th century it became apparent that there was an increasing number of cases of human cystic echinococcosis (CE) being recorded Kazakhstan. Official government statistics document an increase in cases of CE from about 200 cases per year until 1994, rising rapidly to approximately 1000 cases per year by the beginning of the 21st century. This epidemic emerged at a time of rapid economic decline, and decreases in medical services (Torgerson *et al.*, 2002) and hence was unlikely to be an artefact caused by improved diagnosis.

This review gives an overview of more recent data concerning the reported cases of human cystic echinococcosis in Kazakhstan. We also review the data available for *E. granulosus* infection in animal hosts. There is less evidence with regard to human alveolar echinococcosis. However, analysis of data from hospital records of a referral centre in Almaty indicates it could be an increasing problem. Likewise cases recorded in Kazakstani expatriates, now resident in Germany also indicates that human AE in Kazakhstan is far from negligible. Finally we also review data on infection with *Echinococcus multilocularis* in animal hosts.

Notified human cases of echinococcosis

Echinococcosis is a notifiable disease in Kazakhstan and official government figures document a mean of 850 cases per year between 2007 and 2013. This varied between 917 cases notified in 2010 to 802 cases notified in 2013. The mean incidence of notified cases over this period was 5.1 cases per 100,000 per year. Most cases are seen in the southern regions of Kazakhstan where the annual incidence is over 10 cases per 100,000 in Zhambyl and South Kazakhstan Oblasts (Figure 1). However there is substantial numbers reported in western regions (up to 7 cases per 100,000). Even in some areas which were thought of as low endemicity such as in Northern Kazakhstan Oblast, there is now reported an incidence of 3.2 cases per 100,000 (Figure 1). The data base does not generally distinguish between the two types of echinococcosis (which could include CE and AE). However, 4 cases of “alveococcosis”, assumed to be AE were notified in the data base between 2007 and 2013.

Hospital records of echinococcosis and estimates of AE incidence

The notified data either does not differentiate between AE and CE or AE is largely not reported. However, AE is an emergent disease in neighbouring Kyrgyzstan (Usubalieva *et al.*, 2013). Furthermore, contact with dogs infected with *Echinococcus multilocularis* is believed to be an important risk factor for human AE, and high prevalences of *E. multilocularis* in dogs have been reported in some communities in south eastern Kazakhstan (Torgerson *et al.*, 2009). Consequently for one major referral centre in Almaty (The Sizganov National Scientific Surgical Centre), the hospital records for echinococcosis were examined to see if there was evidence of human AE. All cases of echinococcosis were examined between 2006 and 2014 (Figure 2). CE and AE were differentiated on clinical grounds (such as by imaging techniques) and AE cases confirmed by histology of resected lesions. Only original case numbers and not treatment episodes were included in the analysis. Between 12 and 58 cases (mean 26.5 cases per year) of CE were treated per year with a total of 301 cases. Of these 168 were female and 133 were male ($p < 0.001$). The mean age of cases was 33.8 years (SE = 0.94). Between 0 and 11 cases (mean of 4 cases per year) of AE were treated with a total of 46 cases. The mean age of AE cases was 35.6 years (SE = 2.0) (range 14 to 58 years). This was not significantly different from the mean age of the CE cases ($p = 0.24$, t test). Of the 46 cases 21 were female and 25 male (NS). Most of these cases – 27, unsurprisingly, were from the Almaty region. However, a number of cases were referred from other regions, often a considerable distance away. In particular, 8 cases were reported from East Kazakhstan region.

Until cases of AE and CE are routinely differentiated in the reporting systems it is not possible to obtain an accurate picture of the incidence of AE. In the reported data, there were 5949 cases of echinococcosis reported between 2007 and 2013. But in the same data base just 4 cases were definitively recorded as AE: 3 in Aqmola Oblast and 1 in Almaty Oblast. This is less than 10% of the total cases reported in one referral centre over the same time period so clearly there is virtually no separate reporting of AE, despite it being a potential problem. However estimates of the incidence of AE can be made. For example if the ratio of CE to AE cases seen in the referral centre was representative of the country as a whole, then $46/301 = 15.3\%$ of the total CE would be an estimate of total AE cases. Modelling uncertainty assuming AE cases and CE cases are presented as a Poisson process, results in a mean of 130 cases per year (95% CIs 93-174 cases) This is an incidence of 0.76 cases (95% CIs 0.54-1.0) per 100,000 per year.

Estimates from data of AE in Kazakhstani Emigrants

An alternative estimate can be made using data reported to the Robert Koch Institute (RKI) in Germany. AE reporting in Germany has been mandatory since 2001. Diagnosis of echinococcosis

by serologic testing and histopathologic examination is reportable to RKI by microbiologic laboratories and pathologists. The data is freely available (Robert Koch Institute, 2002-2014). The data also gives country of origin of each case. In the data base, 6 cases in people of Kazakhstani origin were recorded between 2001- 2013. Using a Poisson model which assumes that the Kazakhstani cases in the RKI data base are notified as a Poisson process, the 6 cases represent an incidence estimate with a 95% confidence intervals (CI) of between 2.2 cases and 13.1 cases over the 13 year period. These CIs were calculated using an internet Poisson CI calculator (see: <http://statpages.org/confint.html>). Then dividing by 13, results in a 95% CI of 0.17 – 1 case per year. However, the data from RKI under estimates the incidence of AE in Germany and was calculated to have a sensitivity of just 33% (CI 25%-40%) (Jorgensen *et al.*, 2008). So the mean annual number of cases and CI can be divided by the sensitivity of the RKI data, again modelling the uncertainty. This results in an estimate of between 0.049 and 0.30 cases per 100,000 annually (mean 0.14) in German residents of Kazakhstani origin as there are 719,000 people resident in Germany with a recent migration history from Kazakhstan (State & Society - 2015). Applying this incidence on Kazakhstani expatriates to the population of Kazakhstan of 17 million, results in an estimate of between 12 and 70 cases per year (mean 34 cases) for Kazakhstan.

***Echinococcus granulosus* in animals**

Previous studies in dogs over 10 years ago indicated a high prevalence in rural dogs. In particular, based on arecoline purgation surveillance studies, village dogs has an estimated prevalence of 5.8% whilst shepherd dogs, more closely associated with livestock activities, had a prevalence of 23% (Torgerson *et al.*, 2003). A study in the small community of Jalanash (located at latitude 46.47, longitude 80.48) in the Tien Shan mountains in southern Kazakhstan, describes a total of 13 of 131 dogs infected with *E. granulosus* (Stefanić *et al.*, 2004). The G1 strain was initially isolated, and G6/G7 strain was also shown to be present by sequencing in 2 of these dogs (Trachsel *et al.*, 2007). This is believed to be the first time the G6/G7 strain has been isolated in Kazakhstan. Further studies in the same community demonstrated 85 of 632 dogs infected with *E. granulosus* with a mean abundance of 812 parasites per dog (Torgerson *et al.*, 2009)

There has also been a study of 41 wolves, necropsied between 2001 and 2008. These wolves were from the southern regions of Kazakhstan – South Kazakhstan, Zhambyl and Almaty Oblasts which correspond to areas where most cases of human CE are described (Figure 1). Of these 8 were infected (c20%) with *E. granulosus* and the mean abundance was 1275 parasites (CIs 405-2342) per wolf (Abdybekova & Torgerson, 2012).

In sheep the mean prevalence of infection has been estimated to be up to 48% in Almaty and 34% in Zhambyl and South Kazakhstan. The mean abundance of infection being 4.7 cysts per sheep

and 2.54 cysts per sheep respectively. Cattle, whilst being infected appear to have a lower prevalence (7.2%) and lower abundance of infection (0.48 cysts per animal) (Torgerson *et al.*, 2003). In this study the infection pressure was estimated through mathematical modelling as 1.98 cysts per sheep per year in Almaty Oblast, 1.24 cysts per year in Zhambyl and South Kazakhstan Oblasts and 0.15 cysts per year for cattle.

***Echinococcus multilocularis* in animals**

E. multilocularis has been described in two reports in dogs. In 2004 (Stefanić *et al.*, 2004) described 6 dogs from a sample of 131 (from Jalanash - see above), were proven to be infected with *E. multilocularis*. One of these dogs was co infected with *E. granulosus* and is one of the first reports to confirm both species of parasite co infecting the same dog. Further studies in the same district demonstrated 29 dogs from 632 sampled (5%) were infected with *E. multilocularis* (Torgerson *et al.*, 2009). In an extensive review (Shaikenov, 2006) describes the ecology of *E. multilocularis* in Kazakhstan. The parasite is distributed over much of Kazakhstan, but with a patchy distribution in arid areas. Rodents in such areas are more likely to be infected if they inhabit ecological niches where there is higher humidity such as desert oases or river valleys. In more humid mountain areas and northern steppes, the distribution appears to be more extensive. A large number of intermediate hosts from the genera *Marmota*, *Lagurus*, *Microtus*, *Ondatra*, *Apodemus*, *Rhombomys*, *Meriones*, *Allactaga*, *Cricetulus* and *Clethrionomys* are recorded as being infected. Two fox species: the red fox *Vulpes vulpes*, and the corsac fox *Vulpes corsac* are the main definitive hosts.

Conclusions

E. granulosus is widely distributed in Kazakhstan with human cases of CE and animal infection, in both dogs and livestock being widespread. The reported human incidence of echinococcosis appears to have stabilized at between 800 and 1000 cases per year following a rapid increase in incidence in the last decade of the 20th century. The situation with regard to AE is less clear. Infection in wild animal hosts has long been known, however the reports of dogs becoming infected represent a potential greater risk to humans because of the closer contact between dogs and humans. The evidence in this review does suggest that there are significant numbers of cases of human AE in Kazakhstan. The estimate of 130 cases per year based on hospital records and the ratio of AE:CE cases could overestimate the number of cases as the referral centre tends to deal with more complex cases of Echinococcosis and AE has more severe sequelae than CE. Likewise the 34 cases per annum, estimated from an emigrant population may not be representative because this population of emigrants are mainly of German descent, who were offered German citizenship after the dissolution of the Soviet Union. Furthermore, Germany is endemic for AE, so it is possible that some cases in

the emigrant population were infected in Germany. However because of the very long latent period of AE before clinical signs appear, then clinical AE in recent immigrants is likely to be a result of infection outside of Germany. It is essential therefore that comprehensive monitoring for human AE is initiated, especially in light of the on going epidemic of human AE now being reported in Kyrgyzstan.



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Legend for Figures

Figure 1. The incidence of reported cases of echinococcosis (cases per 100,000 per year) reported for each Oblast (region) of Kazakhstan. The relative shadings indicate the mean annual incidence of the 7 years 2007 to 2013 inclusive. The data for the city administrations of Astana and Almaty have been merged with Aqmola and Almaty Oblasts respectively.

Figure 2. Numbers of cases of cystic (CE)  and alveolar (AE)  echinococcosis cases treated in a single referral hospital in Almaty between 2004 and 2014.

